

- IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

13, 2000, thus, invention claimed in this application was made prior to January 13, 2000, which is a date earlier than the effective date of the reference.

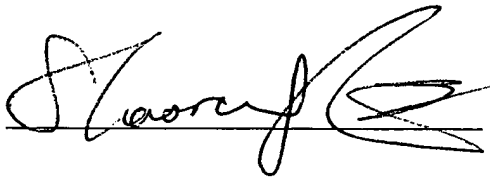
4. From the accompanying document, it is clear that the inventor had constructive reduction to practice of the invention in this application before January 13, 2000.
5. This declaration is submitted prior to final rejection.

As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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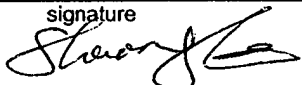
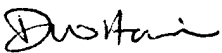
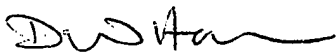
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title of invention/idea Design of A Pseudo Radial Chip		
inventor(s) / author(s) 1 Shaorong Liu 2	signature 	date (ccyy-mmm-dd)
R&D site Sunnyvale, CA, USA		
tel no 408 737 4835		
read and witnessed 	signature	date (ccyy-mmm-dd)
approval of registration 	signature (Science Director)	date (ccyy-mmm-dd)
approval to file IP application	signature (IP Director)	date (ccyy-mmm-dd)

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1. Product or process to which invention/idea may be applied

DNA sequencer and other high throughput assay instruments

2. Laboratory notebook references

3. Background references

See attached description

4. Attachments

Design of A Pseudo Radial Chip

5. Commercial value of the invention/idea to the company

(Brief assessment to be completed by Business Area)

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6. Description of idea/invention and proposed method for putting into practice.

See attached.



Design of A Pseudoradial Chip

Background

The initiatives to complete the sequence of the human genome by 2003¹ and the draft sequence as early as by Spring 2000² demand cost effective high-throughput, high-performance sequencing technologies. DNA sequencing separations have traditionally been performed on slab gels.³ Recently capillary array electrophoresis (CAE)⁴⁻⁹ has been demonstrated to be a high-speed, high throughput method for DNA sequencing. CAE instrumentation is being adapted in leading genomics centers to complete the human genome sequence. The throughput of a CAE system is directly proportional to the number of separation capillaries in the instrument. However, as the number of capillaries increases, it becomes more challenging to control sample injection and detect signals from all the capillaries.

An even more advanced alternative technology for high-throughput DNA analysis is capillary array electrophoresis on microchips. Because photolithographic techniques are used to make CAE microchips, additional capillaries can be readily added. Microchips have analyzed oligonucleotides and RNA, and genotyped and sequenced DNA. The analyses are extremely rapid, from less than a minute for oligonucleotides¹⁰ to about 20 minutes for DNA sequencing.¹¹

Photolithographic technologies were introduced to microfabricate electrophoretic separation channels by Manz and co-workers in 1992.¹² Microfabricated capillary electrophoresis (CE) devices have been used to separate fluorescent dyes,^{13,14} fluorescently-labeled amino acids,¹⁵⁻¹⁸ DNA restriction fragments,^{19,20} PCR products,^{19,21} short oligonucleotides,²² short tandem repeats,²³ and DNA sequencing fragments.^{11,24,25} Separations on CE chips are extremely rapid and are normally complete in seconds to minutes while ultrahigh speed separations can be finished in milliseconds²⁶ or submilliseconds.²⁷ The most recent

results¹¹ on high-speed DNA sequencing used a 7-cm-long electrophoresis channel to separate 500 bases in four-colors with an accuracy of >99% in 20 min. While this demonstrated the fundamental feasibility of four-color DNA sequencing on microfabricated devices, high throughput, multichannel DNA sequencing was not achieved since only a single channel was used.

To increase throughput, CAE channels have been microfabricated on microchips and successfully used for DNA fragment size analysis.^{24,28-30} Channels on these devices have right angle turns that work well for fragment sizing but degrade sequencing separations. We have recently designed a 16-straight-channel chip³¹ which has been used successfully for DNA sequencing. In this design, sample and waste reservoirs are all arranged in a line and evenly spaced at 4.5-mm intervals to facilitate the application of a commercial 8-channel pipettor for sample loading. However, it is very challenging to arrange 96 or more such channels on this chip. In another design,³² 96 straight channels without turns were fabricated on a 10-cm-diameter CAE chip extending radially from the center of the chip where a common anode reservoir is located. The sample, waste, and cathode reservoirs except anode reservoir were arranged around the circumference of the chip. This design, combined with a rotary scanning detection system, provides unique features: (1) chip space is effectively used; (2) the detector scans perpendicularly across all separation channels; and (3) all channels can be designed to be identical to facilitate uniform sample injections and separations. The disadvantage of this design is the separation channel length is limited to less than half of the chip diameter: only 3.3 cm effective separation length was obtained on a 10-cm-diameter device. out of a 10-cm-diameter device.³² Channels of this dimension work well for separations of certain restriction fragments and genotyping samples.³² It is very but it is challenging to achieve sequencing separations

using such short channels. One way to obtain long separation channels is to make huge chips. The disadvantage is the fabrication cost.

Invention

This invention is depicted in Figure 1 to 3. Long separation channels are fabricated on a regular sized chip as shown in Figure 1. All channels are arranged in a fan area. This chip is then diced into a fan shape as indicated in Figure 2. The angle of that fan should be smaller than 180° to make the final channel longer. Three or more of these chips are assembled to form a pseudoradial chip as shown in Figure 3. Figure 1 to 3 present only one example of this invention. Figure 4 present a few examples of how reservoirs and channels are arranged.

Advantages

- a. Channel lengths are doubled;
- b. The number of separation channel is quadrupled due to the increased surface area;
- c. Only a portion of the pseudo radial chip needs to be replaced if one channel is not performing well;
- d. Fabrication cost is minimized.

References

1. Mullikin, J.C.; McMurray, A.A. Sequencing the Genome, Fast. *Science* **1999**, 283, 1867-8
2. Pennisi, E. Academic Sequencers Challenge Celera in a Sprint to Finish. *Science* **1999**, 283, 1822-3
3. Smith, L. M.; Sanders, J. Z.; Kaiser, R. J.; Hughes, P.; Dodd, C.; Connell, C. R.; Heiner, C.; Kent, S. B. H.; Hood, L. E. *Nature (London)* **1986**, 321, 674-679
4. Mathies, R.A.; Huang, X.C. *Nature (London)* **1992**, 359, 167-169
5. Takahashi, S.; Murakami, K.; Anazawa, T.; Kambara, H. *Anal. Chem.* **1994**, 66, 1021-1026

6. Ueno, K.; Yeung, E.S. *Anal. Chem.* **1994**, *66*, 1424-31
7. Dovichi, N. J. *Electrophoresis* **1997**, *18*, 2393-2399
8. Kheterpal, I.; Mathies, R. A. *Anal. Chem.* **1999**, *71*, 31A-37A
9. Mansfield, E. S.; Vainer, M.; Harris, D. W.; Gasparini, P.; Estivill, X.; Surrey, S.; Fortina, P. *J. Chromatogr.* **1992**, *593*, 253-258
10. Effenhauser, C. S., Paulus, A., Manz, A., Widmer, H. M., *Anal. Chem.* **1994**, *66*, 2949-2953.
11. Liu, S.; Shi, Y.; Ja, W.W.; Mathies, R.A. *Anal. Chem.* **1999**, *71*, 566-573
12. Manz, A.; Harrison, D. J.; Verpoorte, E. M. J.; Fettingner, J. C.; Paulus, A.; Ludi, H.; Widmer, H. M. *J. Chromatogr.* **1992**, *593*, 253-258
13. Harrison, D. J.; Manz, A.; Fan, Z.; Ludi, H.; Widmer, H. M. *Anal. Chem.* **1992**, *64*, 1926-1932
14. Jacobson, S. C.; Hergenroder, R.; Koutny, L. B.; Warmack, R. J.; Ramsey, J. M. *Anal. Chem.* **1994**, *66*, 1107-1113
15. Harrison, D. J.; Fluri, K.; Seiler, K.; Fan, Z.; Effenhauser, C. S.; Manz, A. *Science* **1993**, *261*, 895-897
16. Effenhauser, C. S.; Manz, A.; Widmer, H. M. *Anal. Chem.* **1993**, *65*, 2637-2642.
17. Jacobson, S. C.; Hergenroder, R.; Moore, A. W.; Ramsey, J. M. *Anal. Chem.* **1994**, *66*, 4127-4132
18. Hutt, L. D.; Glavin, D. P.; Bada, J. L.; Mathies, R. A. *Anal. Chem.* **1999**, *71*, 4000-4006
19. Woolley, A. T.; Mathies, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*:11348-11352
20. Jacobson, S. C.; Ramsey, J. M. *Anal. Chem.* **1996**, *68*, 720-723

21. Waters, L. C.; Jacobson, S. C.; Kroutchinina, N.; Khandurina, J.; Foote, R. S.; Ramsey, J. M. *Anal. Chem.* **1998**, 70, 5172-5176
22. Effenhauser, C. S.; A. Paulus, A. Manz, and H. M. Widmer. *Anal. Chem.* **1994**, 66, 2949-2953
23. Schmalzing, D.; Koutny, L.; Adourian, A.; Belgrader, P.; Matsudaira, P.; Ehrlich, D.; *Proc. Natl. Acad. Sci. U. S. A.* **1997**, 94, 10273-10278
24. Woolley, A. T.; Mathies, R. A. *Anal. Chem.* **1995**, 67, 3676-3680
25. Schmalzing, D.; Adourian, A.; Koutny, L.; Ziaugra, L.; Matsudaira, P.; Ehrlich, D. *Anal. Chem.* **1998**, 70, 2303-2310
26. Jacobson, S. C.; Hergenroder, R.; Koutny, L. B.; Ramsey, J. M. *Anal. Chem.* **1994**, 66, 1114-1118
27. Jacobson, S. C.; Culbertson, C. T.; Daler, J. E.; Ramsey, J. M. *Anal. Chem.* **1998**, 70, 3476-3480
28. Woolley, A. T.; Sensabaugh, G. F.; Mathies, R. A. *Anal. Chem.* **1997**, 69, 2181-2186
29. Simpson, P. C.; Woolley, A. T.; Mathies, R. A. *Biomed. Microdevices* **1998**, 1, 7-26
30. Simpson, P. C.; Roach, D.; Woolley, A. T.; Thorsen, T.; Johnston, R.; Sensabaugh, G. F.; Mathies, R. A. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, 95, 2256-2261
31. Liu, S; Ren, H; Gao, Q; Roach, D; Loder, B; Armstrong, T; Mao, Q; Blaga, I; Barker, D; Jovanovich, S. Manuscript submitted. **1999**
32. Shi, Y.; Simpson, P. C.; Scherer, J.R.; Wexler, D.; Skibola, C.; Smith, M. T.; Mathies, R.A. *Anal. Chem.* Accepted, **1999**

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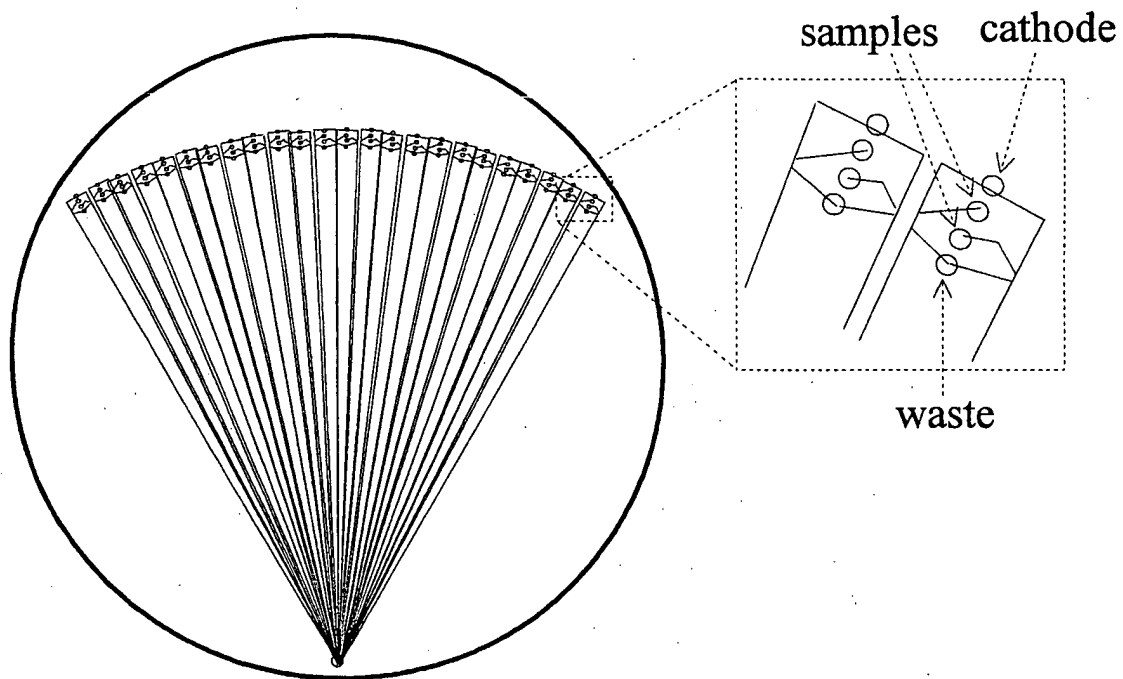


Figure 1. A schematic design of a long separation channels on a regular sized chip



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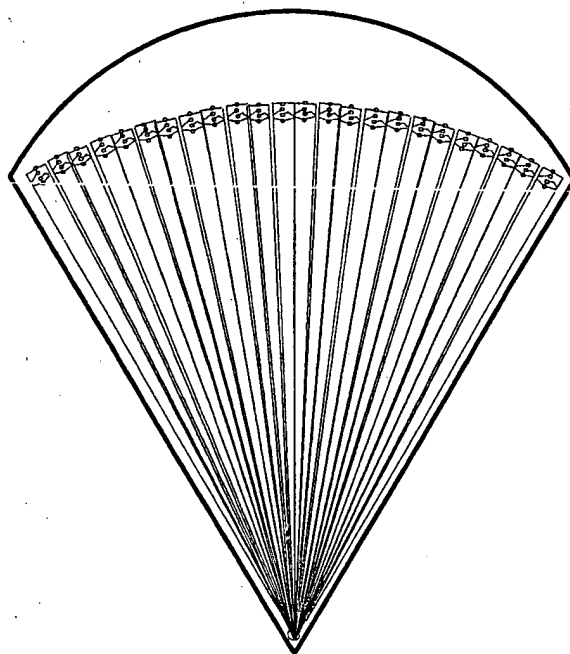


Figure 2. The chip being diced

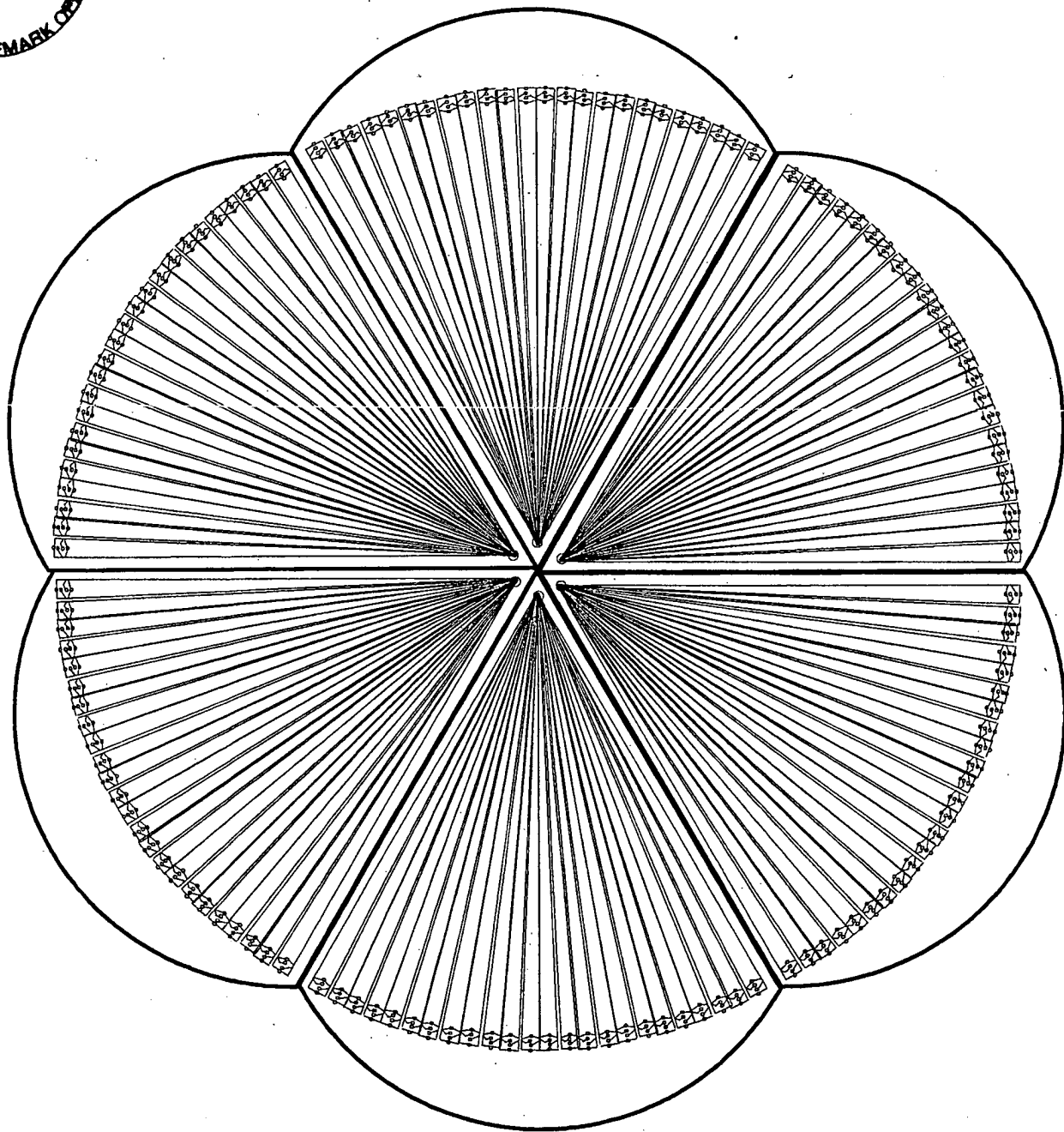


Figure 3. A schematic diagram of a pseudo radial chip



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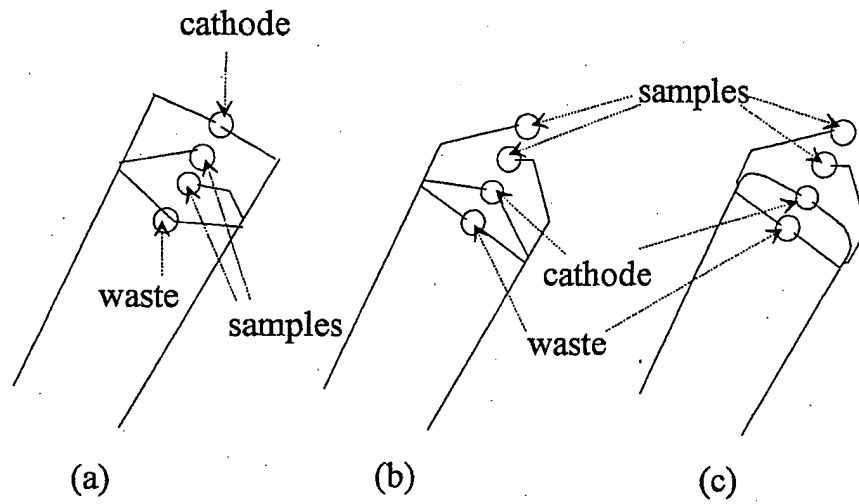


Figure 4. Examples of reservoir and channel arrangements